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L12: Entry 1 of 5 File: USPT Feb 11, 2003

US-PAT-NO: 6518261
DOCUMENT-IDENTIFIER: US 6518261 B2

TITLE: Use of eugenol in combination with other chemopreventative agents as prophylaxis for cancers

DATE-ISSUED: February 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Slaga; Thomas J.	Austin	TX		
Kumar; Addanki P.	Denver	CO		
Alworth; William	New Orleans	LA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
Oncology Sciences Corporation	Austin	TX			02

APPL-NO: 09/ 780269 [PALM]
DATE FILED: February 9, 2001

PARENT-CASE:
CITATION TO PRIOR APPLICATION This is a continuation-in-part with respect to U.S. application Ser. No. 09/527,283, filed Mar. 17, 2000, now abandoned, from which priority is claimed under 35 U.S.C. .sctn.120 and under provisions of the Patent Cooperation Treaty. This is also a continuation-in-part with respect to U.S. application Ser. No. 09/777,151, filed Feb. 5, 2001, which is also a continuation in part of U.S. application Ser. No. 09/527,283, filed Mar. 17, 2000.

INT-CL: [07] A61 K 31/56, A61 K 31/075

US-CL-ISSUED: 514/171; 514/720
US-CL-CURRENT: 514/171; 514/720

FIELD-OF-SEARCH: 514/171, 514/720

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5958892	September 1999	Mukhopadhyay et al.	514/44
☐	6136992	October 2000	Ram et al.	552/614

FOREIGN PATENT DOCUMENTS

FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
96/30012	October 1996	WO	
99/22728	May 1999	WO	

OTHER PUBLICATIONS

Sukumaran et al., "Inhibition of tumor promotion in mice by eugenol". Indian J. Physiol. Pharmacol., vol. 38(4), pp. 306-308, 1994.

ART-UNIT: 1616

PRIMARY-EXAMINER: Badio; Barbara P.

ABSTRACT:

The use of eugenol, alone and in combination with 2-methoxyestradiol (2-ME) in the context of prostate cancer prophylaxes and treatment.

4 Claims, 2 Drawing figures

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Search Results - Record(s) 1 through 5 of 5 returned.

1. 6518261 . 09 Feb 01; 11 Feb 03. Use of eugenol in combination with other chemopreventative agents as prophylaxis for cancers. Slaga; Thomas J., et al. 514/171; 514/720. A61K031/56 A61K031/075.

2. 5330771 . 29 Oct 92; 19 Jul 94. Use of eugenol in chewing gum as an antioxidant. Barkalow; David G., et al. 426/3; 426/541 426/651. A23G003/30.

3. 4336258 . 26 Sep 80; 22 Jun 82. Derivatives of eugenol as medicaments. Blum; Jean. 514/356; 546/322 546/326. A61K031/44 A61K031/465 A61K031/455 C07D211/90.

4. WO 9309770 A1 . 12 Nov 92. 27 May 93. BACTERICIDAL PHARMACEUTICAL COMPOSITION CONTAINING CHLORHEXIDINE AND EUGENOL. LUC, JOELLE, et al. A61K031/085; A61K031/155.

5. RU 2000793 C1 . Medicinal herb mixt. with antidiabetic properties - based on Laurus nobilis, with additional eugenol basil, burnet and stevia. CHEREVATYI, B S, et al. A61K035/78.

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Terms	Documents
L11 AND EUGENOL.TI.	5

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L12: Entry 1 of 5 File: USPT Feb 11, 2003

DOCUMENT-IDENTIFIER: US 6518261 B2
TITLE: Use of eugenol in combination with other chemopreventative agents as prophylaxis for cancers

Abstract Text (1):
The use of eugenol, alone and in combination with 2-methoxyestradiol (2-ME) in the context of prostate cancer prophylaxes and treatment.

Brief Summary Text (15):
It is another object of the present invention to provide a method by which the known substance of eugenol may be employed in a new and unobvious manner in the prevention and/or treatment of cancers, including prostate cancer.

Brief Summary Text (16):
It is another object of the present invention to provide a method by which the known substance of eugenol may, in combination with synergistic compounds, including 2-ME, be employed in the prevention and/or treatment of cancers, including prostate cancer.

Brief Summary Text (17):
In satisfaction of these and related objects, disclosed and claimed herein is the use of eugenol, alone and in combination with 2-methoxyestradiol (2-ME) in the context of prostate cancer prophylaxes and treatment.

Brief Summary Text (18):
Eugenol is a major component of the essential oils from bay leaves and the buds of cloves (Eugenia Caryophyllata). It is widely used as a flavoring agent in food products, pharmaceuticals products and also as an analgesic in dentistry. However, nothing has been heretofore known about eugenol's capacity for preventing and treating cancer.

Brief Summary Text (19):
The use of eugenol either alone or in combination with 2-ME offers the following important advantages: i) since eugenol has been used as an analgesic successfully in the dentistry, toxicity is unlikely; (ii) cell cycle analysis data indicated that eugenol inhibited the growth of suspect cells without any significant alterations in the cells cycle profile, thereby indicating a different mechanism of action than that of 2-ME when used in the same context; (iii) yet, eugenol demonstrated synergistic activity with 2-ME. The present inventors have shown that 2-ME inhibits the growth of cells by inducing apoptosis and blocking cells in G2/M phase. Therefore induction of cell death pathway by 2-ME and growth inhibition by eugenol through a different pathway presents a tremendous new weapon for use in preventing and combating cancer.

Drawing Description Text (2):
FIG. 1 is a graphical depiction of data establishing that eugenol inhibits the growth of LNCaP cells significantly--a concentration of approximately 0.75 mM being necessary to see 50% inhibition of growth of LNCaP cells--whereas a concentration of more than 2 mM was necessary to see similar effect in DU145 cells.

Drawing Description Text (3):
FIG. 2 is a graphical depiction of the percent growth inhibition of multiple cell line series, comparing 2-ME alone, eugenol alone and 2ME-combined with eugenol.

Detailed Description Text (2):
The present inventors have used androgen-dependent (LNCaP) and androgen-independent

(DU145) human prostate cancer cell lines to investigate the effect of eugenol and isoeugenol on cancer treatment. These cells were treated with different concentrations of eugenol (0.5, 1, 3, 5 and 10 mM). Cell growth was monitored every 24 hours by counting the increase in the cell number using trypan blue exclusion assay. These results were also confirmed by using cell proliferation assay kit.

Detailed Description Text (3):
As shown in FIG. 1, eugenol inhibited the growth of LNCaP cells significantly. A concentration of approximately 0.75 mM was necessary to see 50% inhibition of growth of LNCaP cells whereas a concentration of more than 2 mM was necessary to see similar effect in DU145 cells.

Detailed Description Text (4):
The investigational work of the present inventors also establish that eugenol works in combination with 2-ME to achieve even more impressive results. Cells were treated with either eugenol (0.25, 0.5, 0.75 or 1 mM) or 2-ME (0.5, 1, 2 or 3 mM) or both (0.25, 0.5, 0.75 or 1 mM of eugenol along with 0.5 mM of 2-ME). Cell growth was measured following 72 hours of treatment as described above. As shown in FIG. 2, 0.5 mM of 2-ME inhibited growth of LNCaP cells by about 20% and 0.25 mM of eugenol inhibited the growth by about 30%. However, combining both the agents showed more than 50% inhibition thereby establishing a synergistic activity of eugenol and 2-ME in combating cancer cells.

Detailed Description Text (5):
The mechanisms of action at work against the cell lines investigated thus far are reasonably expected to be equally efficacious in treating other cancers and pre-cancerous conditions, such BPH and the cancers of brain, liver, lung, colon and skin. Since both hormone-responsive and hormone-refractory prostate cancer cells are inhibited by eugenol, patients can be treated with eugenol after surgery to prevent the recurrence of hormone-refractory cancer. As indicated, the synergistic effects of eugenol and 2-ME provide an even more potent weapon against cancers.

Detailed Description Text (6):
Application to existing, in vivo tumors may be of varying means, including, but not limited to, direct injection, electrophoresis, and non-electromotive transdermal migration. Practitioners skilled in the use of chemopreventative agents will adjust dosages to meet the apparent needs of any particular patient, and the disclosure contained herein shall provide an enabling disclosure for the use of eugenol alone, and with the synergistic compound of 2-ME in the treatment or prevention of cancerous tumors.

Other Reference Publication (1):
Sukumaran et al., "Inhibition of tumor promotion in mice by eugenol". Indian J. Physiol. Pharmacol., vol. 38(4), pp. 306-308, 1994.

CLAIMS:

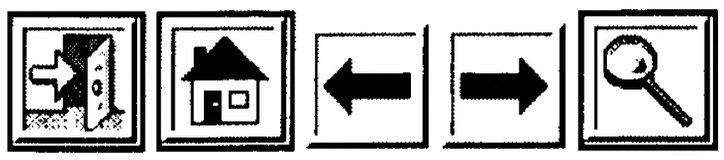
1. A method for inhibiting the growth of cancerous and precancerous cell populations comprising the step of applying a therapeutic amount of eugenol and 2ME in combination to a cancerous or pre-cancerous prostate cell population for a sufficient time to observe arrest of growth of said population.

2. A therapeutic agent useful in the prevention and treatment of prostate cancerous tumors comprising therapeutic dossages of eugenol and 2-methoxyestradiol in combination.

3. A method of inducing apoptosis in cancerous tissues comprising the steps of: administering a therapeutic dosage of a composition containing 2-methoxyestradiol and eugenol in combination to a cancerous or pre-cancerous prostate tissues, said administration continuing at least until the initiation of cell apoptosis in said cancerous tissues.

4. A method for arresting growth of cancer tissues comprising the steps of: administering a therapeutic dosage of a composition containing 2-methoxyestradiol and eugenol in combination to a cancerous or pre-cancerous prostate tissue, said

administration occurring at a time wbich, at least for some cells in said cancerous tissue, precedes cell division in the G2/M phase.



Long View for STIC Online Catalog

Your Search: **ISSN = 1043-6618**

Displaying Record: **1 of 1**

Title	Pharmacological research : the official journal of the Italian Pharmacological Society.
Imprint	London ; San Diego : Academic Press, c1989-
Dates of Pub	Vol. 29, no. 1 (Jan./Feb. 1994)-
Description	v. : ill. ; 24 cm. Pharmacological research communications
Contributors	Società italiana di farmacologia.
Frequency	Bimonthly
Notes	"Available on ADONIS, v. 29-37- (1994-1998)." Title from cover.
Subjects	Drugs --Research--Periodicals. Pharmacology --Periodicals.
ISSN	1043-6618

Biotechnology and Chemical Library	ADONIS		Available
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Biotechnology and Chemical Library	RS122 .P45	v.33 no.1-6 (1996 JAN-JUN) c.1	Available
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Biotechnology and Chemical Library	RS122 .P45	v.35 no.1-4 JAN-APR 1997 c.1	Available
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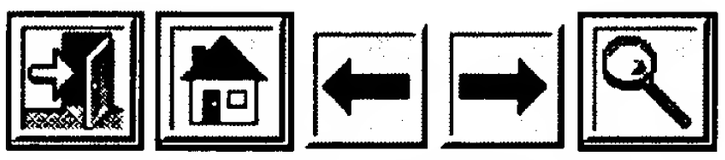
Biotechnology and Chemical Library	RS122 .P45	v.37 no.1-6 JAN-JUN 1998 c.1	Available



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